Aortic Endograft Infection with *Mycobacterium chimaera* and *Granulicatella adiacens*, Switzerland, 2014

Andreas Plate, Thomas A. Kohl, Peter M. Keller, Sabine Majer, Rosamaria Fulchini, Carol Strahm, Cristoforo Medugno, Zoran Rancic, Lars Husmann, Hugo Sax, Stefan Niemann, Barbara Hasse

We describe an aortic endograft infection caused by *Mycobacterium chimaera* and *Granulicatella adiacens*, successfully treated with prolonged antimicrobial drug therapy after complete explantation of the infected endoprosthesis and extra-anatomical reconstruction. Whole-genome sequencing analysis did not indicate a close relationship to bacterial strains known to cause infections after cardiac surgery.

Aortic endograft infection (AGI) is a serious complication of aortic repair, and treatment involves prolonged antimicrobial drug therapy and complete or partial graft explantation with subsequent in situ or extra-anatomic arterial reconstruction. AGI attributable to nontuberculous mycobacteria (NTM) is a rare condition, and sporadic cases have been described (*1*). *Mycobacterium chimaera* is a slow-growing NTM and a member of the *M. avium* complex. Recent publications show the emergence of disseminated *M. chimaera* infections occurring after open heart surgery (*2*). A field investigation identified contaminated heater–cooler units (HCUs) as the source of infection (*3,4*). In addition to valve reconstructions, these cases also involved thoracic aortic grafts. We describe an abdominal AGI caused by *M. chimaera* and *Granulicatella adiacens*. Our aim was to find the source of the *M. chimaera* infection by using whole-genome sequencing (WGS) to compare the patient's isolate to strains implicated in infections known to occur after cardiac surgery.

Author affiliations: University Hospital Zurich, Zurich, Switzerland (A. Plate, Z. Rancic, L. Husmann, H. Sax, B. Hasse); Research Center Borstel–Leibniz-Center for Medicine and Biosciences, Borstel, Germany (T.A. Kohl, S. Niemann); German Center for Infection Research, Borstel (T.A. Kohl, S. Niemann); National Center for Mycobacteria, University of Zurich, Zurich (P.M. Keller); Institute of Medical Microbiology, University of Zurich, Zurich (P.M. Keller); Cantonal Hospital Münsterlingen, Münsterlingen, Switzerland (S. Majer); Cantonal Hospital St. Gallen, St. Gallen, Switzerland (R. Fulchini, C. Strahm); Cantonal Hospital Frauenfeld, Frauenfeld, Switzerland (C. Medugno)

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The Study

In March 2014, a formerly healthy 60-year-old man underwent an elective endovascular aortic repair because of an infrarenal aortic aneurysm. In May 2015, the patient sought medical care for low back pain radiating into the left leg. Laboratory examinations showed elevated C-reactive protein (57 mg/L [reference range <5 mg/L]), leukocytosis (14.8 g/L [reference range <9 g/L]), and acute kidney injury (estimated glomerular filtration rate 44 mL/min [reference range >80 mL/min]). A ^{18}Fluorodeoxyglucose positron emission tomography–computed tomography (PET–CT) examination indicated an AGI and showed an abscess formation in the iliopsoas muscle in close contact with the left common iliac artery; the intraoperative situs was highly suspicious for AGI, including erosion of the left common iliac artery and a visible endograft. The patient was transferred to the University Hospital Zurich (Zurich, Switzerland) for repeat surgery. The surgical procedure entailed complete endoprosthesis removal, closure of the aortic stump below the renal arteries with polypropylene sutures, and omentum coverage. All tissues were debrided, and treatment included vacuum-assisted open-abdomen treatment. Perfusion of the lower limbs' arteries was maintained with an axillo-bifemoral reconstruction using a polytetrafluoroethylene graft (Figure 1).

Deep wound cultures obtained during surgical revisions revealed *M. chimaera* (in 3/3 cultures) and *Granulicatella adiacens* (in 4/18 cultures). Histopathologic test results were compatible with mycobacterial infection (online Technical Appendix Tables 1, 2, https://wwwnc.cdc.gov/EID/article/24/9/18-0247-Techapp1.pdf). Results of blood cultures and mycobacteriologic blood and sputum cultures remained negative. The patient received a combination therapy containing clarithromycin, rifabutin, ethambutol, and amikacin in the early postoperative phase. After 6 weeks, amikacin was replaced by moxifloxacin. For coverage of *G. adiacens*, amoxicillin was added to the regimen. We treated the patient for a total of 12 months after the extra-anatomic reconstruction. Several PET–CT scans showed a complete metabolic response.

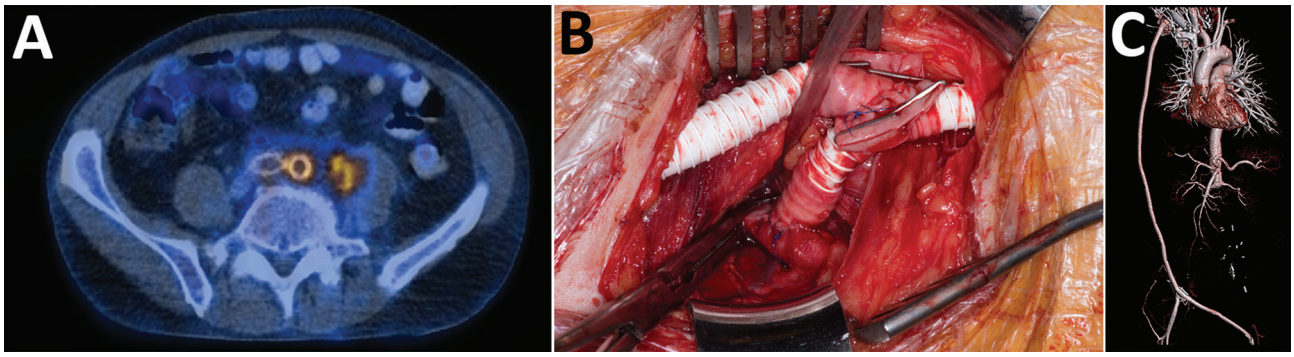

Figure 1. Preoperative, intraoperative, and postoperative images in the case of a patient who received an abdominal aortic endograft and was later diagnosed with *Mycobacterium chimaera* and *Granulicatella adiacens* infection, Switzerland, 2014. A) ^{18}Fluorodeoxyglucose positron emission tomography–computed tomography scan at diagnosis indicating a strong, metabolically active (maximum standard uptake value 9.7) aortic endograft infection and an adjacent abscess formation in the iliopsoas in close contact with the left common iliac artery. B) Intraoperative extra-anatomic position of a polytetrafluoroethylene graft through noninfected subcutaneous operative field. C) Satisfactory postoperative result of the axillo-bifemoral bypass on volume-rendered reconstructions of a contrast-enhanced computed tomography.

The diagnostic workup in May 2015 revealed an incidental 5-mm small pulmonary nodulus in the right upper lobe, which was observed to be metabolically active in PET–CT. After recovery from the abdominal intervention, the patient underwent wedge resection, and a localized squamous-cell carcinoma of the lung was confirmed. In April 2016, a relapse of his neoplasia occurred. Despite intensified chemotherapy, the patient died in August 2017 because of progressive pulmonary cancer; no autopsy was performed.

We cultured mycobacteriologic samples in BD MGIT tubes (BD, Franklin Lakes, NJ, USA) on Middlebrook 7H11 agar plates (BD) according to previously published methods (*3*). Air and water mycobacterial cultures were performed as suggested by the European Centre for Disease Prevention and Control (*5*).

We analyzed WGS data from the patient's isolate and strains from published studies (*2*,*6*–*10*) by using a reference mapping approach with the *M. chimaera* DSM-44623 genome (GenBank accession no. NZ_CP015278.1), aided by Burrows-Wheeler Aligner (http://bio-bwa.sourceforge.net), SAMtools (http://samtools.sourceforge.net/cns0.shtml), and GATK (https://software.broadinstitute.org/gatk) software. We combined variant positions to construct a phylogenetic tree with DnaSP 5.0 (http://www.ub.edu/dnasp/index_v5.html), FastTree (http://www.microbesonline.org/fasttree), FigTree (http://tree.bio.ed.ac.uk/software/figtree), and EvolView (http://www.evolgenius.info/evolview) software (online Technical Appendix).

The HCU-related outbreak of disseminated *M. chimaera* infections led us to investigate the hybrid operating

Table. Microbiologic test results of air and water samples from the operating room where an abdominal aortic endograft was performed on a patient later diagnosed with *Mycobacterium chimaera* and *Granulicatella adiacens* infection, Switzerland, 2014

Sample no.	Type	Place of sampling	Result
1	Water	NaCl heater machine	Negative
2	Water	Respirator 1, suction water tank ID 3393	Negative
3	Water	Respirator 1, breathing hose	Negative
4	Water	Respirator 2, suction water tank	Negative
5	Water	Respirator 2, breathing hose	Negative
6	Water	Operating pre-theater, wash basin, siphon	*M. intracellulare**
7	Water	Operating pre-theater, wash basin, cold water	Negative
8	Water	Operating pre-theater, wash basin, hot water	Negative
9	Water	Operating pre-theater, sink, siphon	Negative
10	Water	Operating pre-theater, sink, cistern	Negative
11	Water	Operating pre-theater, sink, cold water	*M. paragordonae*
12	Water	Scrub room 2, right side, wash basins 1–3, siphon water	Negative
13	Water	Scrub room 2, right side, wash basins 1–3, after flushing	Negative
14	Water	Scrub room 2, left side, wash basins 4–6, siphon water	Negative
15	Water	Scrub room 2, left side, wash basins 4–6, after flushing	Negative
16	Water	Operating pre-theater, sink, warm water	Negative
17	Air	Air sample 1	Negative
18	Air	Air sample 2	Negative
19	Air	Air sample 3	Negative
20	Air	Air sample 4	Negative
21	Air	Air sample 5	Negative

*Misidentification of *M. chimaera* excluded by partial 16S rDNA sequencing.

Figure 2. Phylogeny of isolate from case-patient who received an abdominal aortic endograft and was later diagnosed with *Mycobacterium chimaera* and *Granulicatella adiacens* infection, Switzerland, 2014, and comparison isolates. Maximum-likelihood tree was built from 14,192 single-nucleotide polymorphism positions of 437 group 1 *Mycobacterium chimaera* isolates mapped to the DSM-44623 *M. chimaera* genome (GenBank accession no. NZ_CP015278.1). DSM-44623 is shown as a rectangular phylogram with the inferred subgroups indicated. Inset box shows subgroups 1.8, 1.11, and 1.Branch1, annotated with isolate origin and the source publication. Black arrow indicates position of the patient isolate. Group 1.11 consisted mainly of samples collected at the Maquet production site in Rastatt, Germany (n = 12); 1 isolate came from an in-use Maquet HCU. Branch 1 contained primarily strains from patients with pulmonary *M. chimaera* infections (n = 70) and strains from LivaNova HCUs (n = 4), Maquet HCUs (n = 3), Maquet ECMOs (n = 11), a hospital-built HCU (n = 1), Maquet production site (n = 1), and a patient infected after cardiac surgery (n = 1). ECMO, extracorporeal membrane oxygenation; HCU, heater–cooler unit. Scale bars indicate numbers of substitutions per site.

room where the patient had undergone his initial surgery (online Technical Appendix Figure). The referring hospital did not use HCUs or extracorporeal membrane oxygenation devices. In summer 2015, we obtained water and air samples from the operating room (Table); results were negative for *M. chimaera*.

According to a signature single-nucleotide polymorphism–based classification, the patient isolate was similar to the group 1 strains of *M. chimaera* (*2*). We therefore included all group 1 strains with sufficient WGS data from published studies together with the patient isolate in a combined analysis of a total of 437 strains (Figure 2). The patient isolate did not cluster with subgroup 1.1, which represented all but 1 of the reported cases of disseminated *M. chimaera* infections associated with contaminated HCUs. Instead, the patient strain clustered with strains from subgroup 1.11 and branch 1 of group 1 (*2*); however, the patient strain had no close relationship to any other strain included in the comparison.

The endoprosthetic graft (Excluder RMT261214/PXC121200) of our patient was produced by Gore Medical (Newark, DE, USA). The Swiss Agency for Therapeutic Products submitted a medical device report for the implicated graft to the manufacturer.

Conclusions

We report an endovascular AGI caused by *M. chimaera* and *G. adiacens*, which was successfully treated with extra-anatomic bypass and prolonged antimicrobial therapy. Because of the histopathology results showing focal

granulomatous necrotizing inflammation and detection of sparse acid-fast rods in Ziehl Neelsen stain, we outweighed the importance of *M. chimaera* compared with *G. adiacens*.

Patients at risk for NTM infections are elderly patients with preexisting pulmonary conditions or immunocompromised patients. At AGI diagnosis, the localized pulmonic cancer in this patient was in an early stage, and the patient was not known to be immunocompromised. Blood cultures and repeated sputum specimens were negative for mycobacteria, and PET–CT did not reveal any distant foci. Therefore, we considered a hematogenous spread of a localized and naturally acquired infection to be unlikely. Water and air samples from the operating room were negative for *M. chimaera*; thus, local contamination in the operating room was unlikely. When we compared the patient's isolate with other available *M. chimaera* strains with available WGS data (*2,6–10*), we observed no association with the cardiac surgery cluster or any other closely related strain in the collection. Because the cardiac surgery cluster originated from *M. chimaera*–contaminated water in medical devices, a contamination of the medical prosthesis at the production site was considered, especially because the poorly soluble polytetrafluoroethylene polymerization is conducted as an emulsion in purified water. However, according to the graft manufacturer, its grafts are produced in a controlled environment, and ethylene oxide gas (EOG) is used for sterilization as recommended by the International Organization for Standardization (standard no. 11135-2007). EOG is widely used because of its good bactericidal activity on many bacterial species and even bacillus spores (*11*). However, studies showing the effect of EOG on mycobacteria are lacking, and cases of NTM infections caused by inadequate implant sterilization have been reported (*12*). As the logical next step in the investigation, testing environmental water samples from the production site or from fresh implants for NTM contamination was proposed. However, because of a paperwork assessment, the company decided not to pursue the case further.

Because our investigation involved a single case of an abdominal AGI caused by *M. chimaera* and *G. adiacens*, it is too early to draw any conclusions. If further infections emerge, investigations into the adequacy of EOG sterilization for arterial implants should be conducted. In this case, the combination of prolonged antimicrobial therapy, graft explantation, and extra-anatomic reconstruction resulted in sustained healing.

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About the Author

Dr. Plate is an internal medicine specialist working as an infectious disease fellow in the Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Switzerland. His primary research interests are epidemiology and foreign body–associated infections.

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Address for correspondence: Andreas Plate, University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Raemistrasse 100 CH-8091, Zurich, Switzerland; email: andreas.plate@usz.ch

etymologia

Granulicatella [gran'yoo-lik-ə-tel"ə]

Ronnie Henry

In 1961, Frenkel and Hirsch described strains of streptococci isolated from cases of bacterial endocarditis that grew only in the presence of other bacteria, around which they formed satellite colonies, or in media enriched with sulfhydryl compounds, such as cysteine. These nutritionally variant streptococci were eventually assigned the species *Streptococcus defectivus* (Latin for "deficient") and *S. adjacens* (because it grows adjacent to other bacteria).

On the basis of later research, these were placed in a new genus *Abiotrophia* (Greek *a*, "un-," + *bios*, "life," + *trophe*, "nutrition") as *A. adiacens* and *A. defectiva*. In 1998 and 1999, 2 additional species of *Abiotrophia* were described, *A. elegans* (Latin, "fastidious," referring to fastidious growth requirements) and *A. balaenopterae* (isolated from a minke whale [*Balaenoptera acutorostrata*]). In 2000, these new species, along with *A. adiacens*, were reclassified in the new genus *Granulicatella* (Latin *granulum*, "small grain," + *catella*, "small chain").

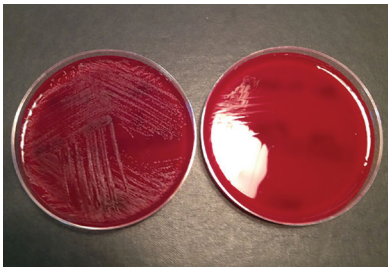

Figure. Blood agar plates with (left) and without (right) pyridoxal supplement from a study of neonatal *Granulicatella elegans* bacteremia, London, UK. Image from Neonatal *Granulicatella elegans* Bacteremia, London, UK; Emerging Infectious Diseases Vol. 19, no. 7, July 2013.

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Address for correspondence: Ronnie Henry, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop E03, Atlanta, GA 30329-4027, USA; email: boq3@cdc.gov

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Technical Appendix

Methods

Whole-Genome Sequencing Analysis

Whole genome sequence data from the patient's isolate and strains from published studies (*1*–*6*) was analyzed by mapping the reads to the *M. chimaera* DSM-44623 genome (NZ_CP015278.1) using BWA and subsequent refinement of the mappings with the SAMtools (http://samtools.sourceforge.net/cns0.shtml) and GATK toolkits (https://software.broadinstitute.org/gatk). For variant detection, we employed SAMtools and minimum thresholds of a coverage of 4 reads in both forward and reverse orientation, 4 reads calling the allele with a phred score of at least 20, and 75% allele frequency. We inferred a group and subgroup classification as described previously (*1*), with manual curation for mixed populations. For further analysis, we included all 437 datasets from group 1 strains, which reached a mean coverage depth of at least 30 fold, with at least 80% of the reference genome complying with the thresholds stated above. For these, detected variant positions were combined, supplementing the joint list with the respective information from the original mappings where necessary. Single nucleotide polymorphism (SNP) positions fulfilling the thresholds for variant detection in at least 95% of the isolates and covered in all samples, were concatenated to a sequence alignment, excluding SNPs within a window of 12 bp from each other in the same isolate.

From the aligned sequences of concatenated SNPs, we identified homoplasious sites with the recombination detection tool implemented in DNASP v5 and removed these sites from the alignment (496 out of 14,688). From the final set of 14,192 SNP positions, we calculated maximum likelihood trees using FastTree version 2 in the Double precision built, with a general

time reversible (GTR) substitution model, 1,000 resamples and Gamma20 likelihood optimization to account for rate heterogeneity among sites. The consensus tree was rooted with the "midpoint root" option in FigTree (http://tree.bio.ed.ac.uk/software/figtree) and annotated using the EvolView software (http://www.evolgenius.info/evolview).

Technical Appendix Table 1. Overview of surgically derived samples and microbiologic/histopathologic results in the patient

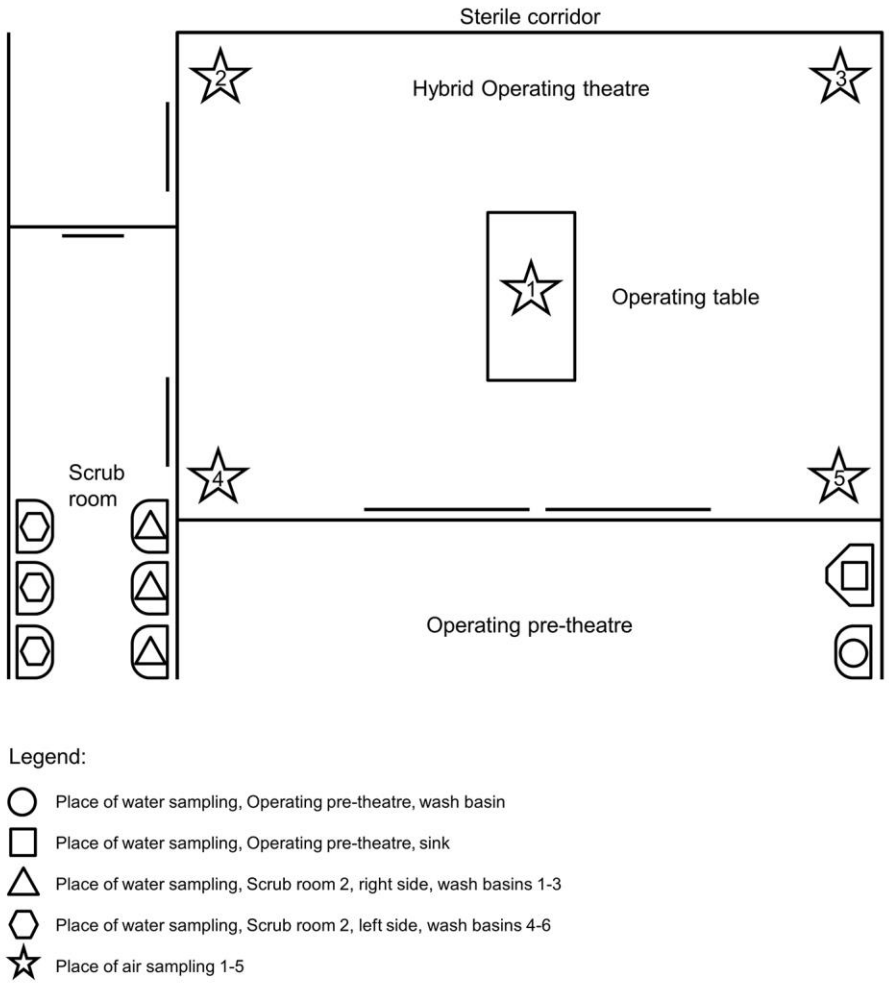
Date	Operation	Specimen	Investigation	Results
22.05.2015	[1,3] Abscess debridement	Deep wound tissue	1/6 Bacteriologic cultures	Coagulase negative Staphylococcus[5]
	[1,4] Coil-embolisation of A. iliaca interna and stent-graft-extension to the left A. iliaca externa		Broad-range PCR Mycobacteriologic culture[2]	Negative *Mycobacterium chimaera.* Time-to-positivity: 9 d
23.05.2015	[1,4] Debridement, NPWT	Deep wound tissue and swab from vascular graft	1/3 Bacteriological cultures	*Granulicatella adiacens.* Time-to-positivity: 5 d
			1/3 Broad-range PCR Mycobacteriologic culture[2]	*Granulicatella adiacens* *Mycobacterium chimaera.* Time-to-positivity: 14 d
			Mycobacterial-genus PCR Histopathology	*Mycobacterium chimaera* M psoas tissue: skeletal muscle and soft tissue with acute inflammation. No evidence of fungi or bacteria. Tissue above graft: necrosis mass. Sparse acid-fast bacilli in Ziehl-Neelsen stain. No evidence of fungi.
29.05.2015	[1,4] Debridement, NPWT	Deep wound tissue and swab from vascular graft	3/3 Bacteriologic cultures	*Granulicatella adiacens*. Time-to-positivity: 3–5 d; MIC Penicillin 0.125 mg/L (S ≤0.25–2 mg/L); MIC Gentamicin 12 mg/L (S ≤2–4 mg/L)
			Mycobacteriologic culture[2]	*Mycobacterium chimaera*. Time-to-positivity: 17 d
			Mycobacterial-genus PCR	*Mycobacterium chimaera*
01.06.2015	[1,4] Endoprosthesis removal. Closure of the aortic stump below the renal arteries. Omentum coverage. NPWT and open abdomen treatment. Axillo-bifemoral reconstruction	Deep wound tissue Vascular graft	6/6 Bacteriologic cultures Mycobacteriologic culture Mycobacterial-genus PCR Histopathology	Negative Not done *Mycobacterium chimaera* Tissue around prosthesis 1: Predominantly necrotic material, old bleeding residuals with adjacent chronic granulomatous inflammation. Tissue around prosthesis 2: Partially calcified soft tissue with chronic granulating, focal granulomatous necrotizing inflammation and detection of sparseacid-fast rods in Ziehl Neelsen stain. Aneurysm sac: Fibrous soft tissue with marginal zone B cell hyperplasia and polytypic plasmocytosis as well as focal chronic granulomatous Necrotizing inflammation. Sparse acid-fast bacilli in Ziehl-Neelsen stain.

Abbreviations: NPWT, Negative pressure wound therapy; MIC; MIC; broad-range PCR, 16S rRNA Gene polymerase chain reaction
Notes: [1] Antimicrobial prophylaxis: At the time of the initial EVAR placement and during the first surgical revisions, the patient received a standard perioperative prophylaxis with Cefazolin 1 g i.v. 20–30 min before the intervention. At the time of the second, third and fourth revision, the patient was under continued antimicrobial therapy and therefore we renounced on perioperative prophylaxis. [2] Only one specimen per surgical procedure was investigated for mycobacteria. [3] Operation performed at the Cantonal Hospital Frauenfeld, Switzerland. [4] Operation performed at the University Hospital Zurich, Switzerland. [5] rated as contamination.

Technical Appendix Table 2. Antimicrobial susceptibility testing of the *Mycobacterium chimaera* patient isolate

Antimicrobial substance	Interpretation
Rifampin	
1 mg/L	S
4 mg/L	S
20 mg/L	S
Rifabutin	
0.1 mg/L	S
0.4 mg/L	S
2 mg/L	S
Amikacin	
1 mg/L	R
4 mg/L	S
20 mg/L	S
Moxifloxacin	
0.5 mg/L	S
2.5 mg/L	S
10 mg/L	S
Clarithromycin	
4 mg/L	S
16 mg/L	S
32 mg/L	S
64 mg/L	S
Ethambutol	
5 mg/L	S
12.5 mg/	S
50 mg/L	S
Linezolid	
1 mg/L	I
4 mg/L	S
16 mg/L	S
Clofazimin	
0.25 mg/L	R
0.5 mg/L	R
1 mg/L	S
4 mg/L	S

Note: In this patient, *M. chimaera* was detected three times by culture with the same AST profile. It is important to note that the terms susceptible (S), intermediate (I), and resistant (R) describe *in-vitro* growth inhibition at a given drug concentration, and are not to be confused with classifications according to clinical breakpoints intended to predict clinical outcome. The intermediate category indicates that the drug concentration examined significantly (>99%), but not completely, inhibits bacterial growth *in-vitro*.



Technical Appendix Figure. Place of sampling at the hybrid operating theater where the endovascular procedure was performed.

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